REMARKS

Applicants have carefully reviewed and considered the explanation of the 2/23/07 Advisory Action and offers the following remarks. Applicants further acknowledge that the earlier 102(b) rejection has been withdrawn.

Currently claims 1-2, 7, 10, 12-17 and 19 have been amended; claims 3, 5-6, 8-9, 11 and 18 have been canceled; as a result, claims 1-2, 4, 7, 10, 12-17 and 19 are now pending in this application.

' 112, First Paragraph Rejection

Claims 15 and 19 were rejected under were rejected under 35 USC ' 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art at the time of the invention that Applicants had possession of the claimed invention, or with which it is most nearly connected, to make and/or use the invention.

Applicants in the instant Background state the following: "Stroke is defined as a sudden, non-convulsive, focal neurological deficit that is related either to cerebral ischemia or hemorrhage." (page 1, lines 18-19). It is well known that clots or thrombi that break loose from upstream locations such as the heart and lungs lodge in cerebral arteries and cause cerebral ischemia. Nevertheless, regardless of the initial cause, the stroke is being treated in this application. However, in a spirit of compromise and in an effort to advance prosecution of this case, Applicants have cancelled the phrase "hemorrhagic or thrombotic" from claim 15, which should obviate the rejection of claim 15 and its dependent claim 19.

§ 103 Rejection of the Claims

Claims 1-4 were rejected under 35 USC § 103(a) as being unpatentable over the Weiss patent (U.S. 5,851,832 - the '832 patent) in view of Sanberg et al. (Abstract 1997) and further in view of Grabowski et al. (1994) as set forth at pages 6-9 of the prior office action.

The Advisory Action reiterates that the '832 patent discloses treatment of neurodegenerative disease (specifically Parkinson's Disease) and brain injuries and further

disclosed in the Background. The Office Action also reiterates that Sanberg et al reference suggest that a greater overall number of transplanted cells is desirable and will produce a better outcome. Moreover, the Office Action states that Grabowski suggests that a longer delay following ischemic injury prior to the transplantation surgery is desirable. The Office Action concludes that all employed widely-accepted rodent models for stroke, so the skilled artisan would have a reasonable expectation of success for treating stroke in humans.

First, to establish a *prima facie* case of obviousness under 35 U.S.C. §103, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the cited prior art references must teach or suggest all of the claim limitations. Furthermore, the suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not based upon the Applicants' disclosure. A failure to meet any one of these criteria is a failure to establish a *prima facie* case of obviousness. MPEP §2143.

Let us start by reviewing the invention and claims under consideration. The Applicants are the first known inventors to inject neuronal cells into humans for the treatment of stroke (subsequent to an arduous preclinical process and filing of an IND). The treatment method includes delivering 2 million viable hNT neuronal cells (or later 6 million cells) to a plurality of brain sites involved in the stroke. The Applicants then followed the patients for a number of months. Only when the patients were evaluable and showed improvement did the Applicants file the instant patent application. The results obtained show that administration of at least six million viable neuronal cells is unexpectedly superior to delivery of two million cells in treating conditions such a stroke, Parkinson's disease, Huntington's disease or trauma which involve brain damage or degeneration.

As indicated in the present application at page 15, measurement of the ESS (European Stroke Scale) in patients showed that after six months the mean change from base line was 1.8 points in the patients given two million viable neuronal cells, indicating no noticeable clinical benefit. However, when the patients were given six million viable neuronal cells, their scores

were much higher at 5.3 points, resulting in a clinical benefit. Thus, the application as filed shows a clear benefit in the use of at least six million viable neuronal cells.

The improved results following transfer of at least six million viable neuronal cells are also seen in the motor elements of ESS indicated at page 16, first full paragraph of the present application. After six months, the mean change from base-line was only 1.9 points for the two million viable cell group, but double that (3.8 points) for the six million viable cell group. As indicated at page 17, first paragraph, the transfer of six million viable neuronal cells also did not cause the rise in systolic blood pressure seen with the transfer of only two million cells.

Thus, as concluded at page 17, final paragraph, of the present application:

> "the stroke scale results suggest that the cells may be efficacious and that the higher dose administered may be more efficacious than the lower dose." (emphasis added)

The superiority of administering at least six million viable neuronal cells shown the application as filed is also further illustrated in the two literature papers Kondziolka (2000) and Kondziolka et al (2002) now submitted. Please note that neither of the papers are prior art, they are submitted as further illustration of the superiority of transfer of at least six million viable neuronal cells demonstrated in the application as filed.

Kondziolka (2000) present some of the results described in the Examples of the present application on which further analysis has been performed. The results obtained are presented in tabular form on page 567 and confirm the improvement in ESS scores shown in the application as filed. In addition, the Table shows that for the Barthel Index (BI) and SF-36, the results seen with administration of at least six million viable neuronal cells is superior to administration of two million cells.

In particular, in comparison to the base line score, the BI after administration of two million viable neuronal cells is actually lowered by over five points; whereas, that for at least six million viable cells is increased by over six points. Similarly for SF-36, the score for two million viable cells is almost three points lower than baseline; whereas, for administering at least six million viable cells the score is increased by over six points in comparison to baseline. Thus, again the transfer of at least six million viable neuronal cells produced unexpectedly superior results in comparison to the transfer of only two million cells.

As indicated on pages 9 to 12 of the instant application, ESS, BI and SF-36 are measures of ability to perform standard life activities, general health and the remaining impact of a stroke. Thus, the improvements seen with six million viable cells are important for improving the ability of victims of stroke to cope with normal life and display recovery.

Kondziolka (2002) is a review article and provides a summary of the advantages of administration of at least six million viable neuronal cells. In particular, Kondziolka et al state at page 227, left hand column, final paragraph, that:

> For the ESS, the increases tended to be larger in the group of four patients receiving six million cells, both in the total scores and in the composite motor sub-scale scores. Both the Barthel Index and the SF-36 scores decreased in the group receiving two million cells and increased in the group receiving six million cells. All outcome measurements were consistent in identifying a trend toward improved scores in the group of patients who received six million neuronal cells."

As stated above, to satisfy the Section 103 requirement of reasonable expectation of success, we need to look at the state of the art at the date of the application filing. The state of the art for treating humans with stroke in 1999 was in fact **dismal**, with no significant hope of success. Rather than being predictable, history shows the failure of others to achieve Applicants' goal. The only treatment was anticoagulants, which had to be administered within three hours of the initial stroke and only to patients with demonstrated non-hemorrhagic strokes. Because of these stringent requirements and the expense, few patients are *still* treated by this method. Treatment after the stroke consisted only of physical therapy.

A recent report summarized the state of art: over 800 drug entities intended to treat stroke had been successful in 4000 animal tests, but NONE were successful in humans. Moreover, Dr. Grotta (Stroke, 2001, 33:306-7) states that "We need to find treatments that are substantially more potent than those that have failed in clinical trials to date." "The failure to translate the positive effects of a variety of neuroprotective strategies [for stroke] from animal models to human trials has perplexed investigators." (Davis and Donnan, 2001, Stroke 33:309-10)

Due to the uniform failure of the translation of the rodent success into human therapy, a number of experts convened and published "Recommendations for Standards Regarding Preclinical Neuroprotective and Restorative Drug Development,", published in 1999 (Stroke 30:2752-2758). Note that this is almost simultaneous with the filing of the instant patent

application. This article provides information on the treatment of acute stroke (neuroprotection) and treatment of stroke recovery. They too affirm the total lack of success:

> "The idea of protecting brain tissue from injury (neuroprotection) is not a new concept. Many neuroprotective agents and strategies were studied in the past, for example, free radical scavengers, excitatory amino acid antagonists, hypothermia, barbiturates, calcium channel blockers, growth factors, and others have been investigated for years. What remains curious is that although many of these agents appear quite effective in preclinical studies with small-animal models of ischemia (rats, mice, or gerbils), none of these have proven conclusively to be effective in humans…" (p. 2752; references omitted; emphasis added)

The committee explored possible reasons for this total failure. First, they considered drug dose. They stated that the drug dose effective in the mouse or rat may not be effective in large animals and/or humans, even after scaling up the dose for increased weight. Another problem they cited was that potentially doses could be most effective at only one of low, medium or high doses and not at other doses. They also mentioned that drug dose ranges and toxicities in animals may not overlap with those tolerated in humans. "Furthermore, rodents, for example, display extraordinary plasticity." (p. 2754) "Recovery in rodent models occurs rapidly over the first few weeks after stroke. Recover in humans with stroke may occur over a longer time, up to several months after stroke." (p. 2756) Contrast these statements with the Office Action that alleged that human dosing is obvious to one skilled in the art. These statements express the failure of those skilled in the art at judging doses.

Another problem the Committee considered was the differences in animal models. The MCAO model (used in some of the Examiner's references) is standard for acute stroke (p. 2754); but they stated the following: "A standard rodent model for post-stroke recovery studies has yet to be established. The histopathology and behavioral deficits seen with global ischemia are quite distinct… Standard methods have yet to be established regarding measurements of animal behavioral deficits and their recovery after focal infarction in rodents." (emphasis added, p. 2756). In addition, "currently there are no standardized, well-accepted models of stroke recovery in primates, although limited experience exists with baboons."

The Committee concluded "there is currently a substantial unexplored opportunity for the development of new pharmacological agents and other treatments to enhance functional recovery

after stroke." (p. 2757) These reports from preclinical stroke experiments evidence the lack of useful models and the failure of animal models to predict utility in humans.

As shown above, Applicants have modified the claims to recite the treatment of stroke in humans using hNT cells. The claims recite the use of at least 6,000,000 viable cells. The following discusses the references in the light of the current claims.

Viewing the '832 reference as a whole, one can see that both rodent (Examples 1-8) and primate cells were processed to produce neurospheres and their progenies, including nerve cells and other nervous tissue cells. In addition, some rodent models were implanted with either embryonic or adult-derived nervous tissue. Moreover, there is a hypothetical example of a "patient" with non-specified "neurodegenerative disease" receiving fetal cells (Example 14). Examples 16 and 17 also are hypothetical examples of the treatment of the demyelinating diseases. Example 18 is a hypothetical example of administration into a human patient in the method described in Example 14. These are all hypothetical examples.

As with the '780 publication, there is no example of successful transplantation into humans, just rodent models which do not have a reasonable expectation of success in providing therapeutic benefit in humans. Thus, although the '832 patent alleges human treatment of neurodegenerative disorders, it provides no details such as are claimed by Applicants. There is no support for the actual use in humans with strokes, no specifics on amount, delivery, etc.

Similarly, the Sanberg et al teachings are based on the implantation of hNT cells in an animal model, and do not provide a reasonable expectation of success in humans. Moreover, Sanberg et al teachings do not disclose other important limitations in the claims, including the number of cells appropriate for human use.

The third reference is Grabowski et al disclosing a rodent model and a different source of cells no longer claimed. Furthermore, while Grabowski alleges that longer delay in administering the cells (as long as 3 months), there is no experimental support for that allegation Therefore, the mere allegation of an unsupported, not reliable allegation does not render obvious the clinical findings of the instant invention. The Office Action also suggests the arguments of nonenablement of this reference suggests "nonenablement of [the Applicants'] own method claim." However, Applicants are the first to demonstrate successful use in humans in time frames of 6 months to 6 years post-stroke, thus enabling the instant claims.

Because the combination of references fails to teaching every limitation of the instant claims 1-4, this ground for rejection appears to be moot and may be withdrawn.

Section 103 Rejection of claims 7-19 Sanberg and Borlongan (1996), in view of the '832 patent and further in view of Uchida (1995).

The Office Action cites the principles: "Even if a reference discloses an inoperative device, it is prior art for all that it teaches." Furthermore, "A non-enabling reverence may qualify as prior art for the purpose of determining obviousness under 35 U.S.C. 103." (references omitted)

The Office Action states that Sanberg and Borlongan reported cognitive function in rats transplanted with hNT cells or striatal cells, similar to what was observed when fetal striatal cells were used in treating neurodegenerative diseases such as Huntington's. The Applicants believe that these proofs are limited to the conclusion that in rodent models for stroke and Huntington's, hNT cells or striatal cells have proven successful. There is no report of use in humans, nor is there any recitation or suggestion of the claims amount in humans.

The Office Action next notes that Uchida et al implanted cells of the same genetic makeup as the recipient is irrelevant because a) there is no recited limitation of non-syngenic cells in the claims and b) this reference was not relied upon for teaching which type of cell of implant (those teachings being found in the '832 patent and Sanberg and Borlongan). Uchida is cited to prove that transplanted cells have the capacity to migrate to distant sites. The Office Action goes on to state that migrating cells in the prior art would render obvious claim 15, wherein it is recited that the cells are implanted "into a location from which the neuronal cells migrate to the damaged area."

The Uchida references also states that "[i]t cannot be ruled out that the 'distant' cells were *deposited at their sites during implantation* (emphasis added)." Therefore, the teachings of Uchida are inconsistent and cannot be used to support the use of Uchida for the proposition that any transplanted cells can migrate to distant sites. Furthermore, the many differences between the cells and recipient, as well as the lack of dosage in Uchida militate against applying this reference to currently amended claim 15.

Taking all the references together, none teach the use of hNT cells to treat stroke in humans, nor do they teach of suggest the proper dosage that is recited. Most successful animal

tests of stroke do not result in success in humans. Therefore, even though the animal model of stroke is popular (because there is no other), it is not a successful predictor for human success in most instances.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (480-344-7745) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 50-3956.

Respectfully submitted,

By their Representatives,

Date Aug 22, 2007

The Luther Law Firm, PLC
12198 E. Columbine Dr.
Scottsdale, AZ 85259

By Barbara J. Luther

Barbara J. Luther
Reg. No. 33,954

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being electronically filed with the United States Patent & Trademark Office on this 22d day of August, 2007.

Chris Dobrowolski

Name

Signature